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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/281,717	03/30/99	BAXTER J	UCAL-253/02U

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EXAMINER	
OGIHARA, N	
ART UNIT	**PAPER NUMBER**
1631	9

DATE MAILED: 06/14/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/281,717	BAXTER ET AL.	
	Examiner	Art Unit	
	Nancy Ogihara	1631	

-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *18-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claims *1-30* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

14) ☒ Notice of References Cited (PTO-892)
15) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
16) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
17) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
18) ☐ Notice of Informal Patent Application (PTO-152)
19) ☐ Other:

DETAILED ACTION

Claims 1-30 are pending in the instant application. Applicant's election with traverse of Group I, claims 1-16 and 30, in Paper No. 6 is acknowledged.

The traversal is on the ground(s) that concurrent examination on the merits of the invention of claims of elected Group I with the invention of the sole claim of Group II would not place a serious burden on the Examiner, and that (a) the inventions must be independent or distinct as claimed and (b) there must be a serious burden on the Examiner if the restriction is not required. Applicant further argues that Groups I and II have been identically classified, that the goals of Group I and II are the same, and the method steps are very similar, and that if the search and examination of the entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes independent or distinct inventions.

The arguments for the rejoinder of Groups I and II are persuasive, as the inventions of both groups are closely related. Therefore, claims 1-17 and 30 will be examined herein.

The requirement of restriction for Groups III-V (claims 18-29) is still deemed proper and is therefore made FINAL.

Claims 18-29 are withdrawn from further consideration as being drawn to a non-elected invention.

Priority

This application claims priority to provisional application 60/113,146 filed 12/16/98 under 35 U.S.C. 119(e).

Oath

The oath is defective for the following reason: the claim to benefit under Title 35, U.S.C. §119(e) should claim priority to provisional application 60/079,956, and not, as is currently written, to 60/079,965. Appropriate correction is required. Until the oath is corrected, the priority date for the instant application is the effective filing date of 12/16/98.

Specifications

If applicant desires priority under 35 U.S.C. 119 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No._____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

Sequence Listing

Examiner acknowledges receipt of the faxed communication dated March 30, 2000 regarding the typographical error in SEQ ID NO: 6 of the sequence listing. The CRF has been corrected accordingly.

Claim Objections

Claim 1 is objected to because of the following informalities: The term "spacially" appears to be misspelled. The correct spelling should be "spatially." Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 1-17 and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling identifying a compound that activates transcription by binding hTR-β and hER-α, does not reasonably provide enablement for identifying compounds by any other method, and fails to enable the scope of the claims.

Although the specification discloses identifying a compound that modulates coactivator binding to a nuclear receptor (hTR-β and hER-α) by way of transcription activation (i.e. binding of GRIP1 to hTR-β or hER-α activates transcription) (see Example 9). The specification offers no other method for identifying if a test compound modulates coactivator binding to a nuclear receptor other than through testing the effects of binding on transcription. The coactivators disclosed in the specification are known to mediate the effects of transcription factors, such as hTR-β and hER-α thus leading to

transcription (See IDS document: Ding et al, Mol. Endo. Vol. 12(2), pp. 302-313, 1998; see Introduction). Identification of compounds that modulate coactivator binding through methods other than through transcription assays is unpredictable for the disclosed class of nuclear receptors. Therefore, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with claims.

Claims 1-17 and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the nuclear receptors with cofactor binding sites such as hTR-β or hER-α, does not reasonably provide enablement for nuclear receptors not containing cofactor binding sites and fails to enable the scope of the claims.

The claims are directed toward identifying a compound that modulates cofactor binding to a nuclear receptor. Although the specification discloses that hTR-β and hER-α contain cofactor binding sites for binding such cofactors as GRIP1 and SRC-1a (see page 16, line 9), it is not clear that the broad group of nuclear receptors (i.e. receptors in the nucleus), other than hTR-β or hER-α, necessarily have cofactor binding sites. Therefore, identifying a compound that modulates cofactor binding, with nuclear receptors other than those disclosed, would be unpredictable and require undue experimentation to attempt when it is uncertain if there is a cofactor binding site. Although there are other nuclear receptors within the same family as those of hTR-β and hER-α, a person of ordinary skill in the art would not readily be able to identify compounds that bind and modulate cofactor binding without undue experimentation. Applicant has merely provided an invitation to experiment. Therefore, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with claims.

Claims 1-17 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 is vague and indefinite because the claim terminology "TR," "RAR," "RXR," "PPAR," "VDR," "ER, " "GR," "PR," "MR," and "AR" should be completely spelled out at its first appearance in a claim and not abbreviated. Appropriate correction is required.

Claim 9 is vague and indefinite because the claim terminology "NR-box" should be completely spelled out at its first appearance in a claim and not abbreviated. Appropriate correction is required

In claim 1, applicant is claiming a method for identifying a compound that modulates coactivator binding to a nuclear receptor, wherein a test compound is modeled spatially into a coactivator binding site, and wherein said test compound is screened for binding to the coactivator binding site and modulating coactivator binding. Applicant appears to be screening compounds using a competition assay, yet is not clearly stating this.

In claim 12, the metes and bounds of the term "biological activity" are unclear since the specification fails to point out what is encompassed by the term. The nuclear receptors encompassed by the claim have different ligand specificities, promoter specificities, and have different effects on transcriptional control, all of which can be interpreted as "biological activity."

Claim 11 is vague and indefinite in the term "high throughput screening." The term "high" is comparative terminology and by itself does not designate unique or distinct value.

Claims 2-8 are vague and indefinite in the recitation of the term "corresponding to residues of human thyroid receptor." Presumably, "corresponding" refers to the results of a sequence alignment procedure between human thyroid receptor and a nuclear receptor of interest. Depending on the alignment algorithm, "corresponding" can be ambiguous, particularly when the sequence identity is low.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-10, 12, 14-17, and 30 are rejected under 35 U.S.C. 102(a) as being anticipated by Darimont et al (Darimont et al, Genes and Development, vol. 12, pp. 3343-3356, 1Nov, 1998).

Darimont et al disclose a method of identifying a compound that modulates coactivator binding to the ligand binding domain of the human TRβ (i.e. a TR receptor) nuclear receptor in which the NR Box 2 peptide (i.e. a test compound) derived from the GRIP1 coactivator protein is modeled to fit spatially into an atomic structural model of a coactivator binding site of interest (see Figure 4). Darimont et al screen, and thus identify, the NR Box 2 peptide in a competition binding assay (i.e. an in vitro biological assay) in the presence of the coactivator GRIP1 (see page 3345, right column), in which the peptide modulates GRIP1 binding to the receptor. Darimont et al therefore meet the limitations of the claims.

Claims 1, 5, 9-10, 12, 15, and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Scanlan et al (International Patent No. WO 97/21993).

Scanlan et al disclose that thyroid receptor (TR) ligands increase (i.e. modulate or agonize) nuclear receptor coactivation such that the binding of the coactivator protein, RIP-140, is enhanced upon binding of the ligand (See Example 3 page 53). Scanlan et al also disclose computational methods for modeling nuclear receptor ligands into a coactivator binding site of interest on the atomic structural model of the TR nuclear receptor (page 65-67). Furthermore, Scanlan et al disclose methods of screening and identifying ligands in assays (i.e. in vitro biological assays) characterized by binding of a ligand to test for binding of a coactivator protein to a coactivator binding site (see Example 3-4 and Table 2, pages 53-54). The methods of Scanlan et al therefore meet the limitations of the claims.

Claims 1, 5, 9-10, 12, 15, and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Glass et al (IDS document: Current Opinion in Cell Biology, vol. 9, pp. 222-232, 1997).

Glass et al disclose a method of identifying a compound that modulates coactivator binding to a nuclear receptor. Glass et al disclose the atomic model of the RXRα ligand binding domain (see Figure 1) to model interaction of co-activator compounds such as SRC-1 and TIF2 (See Figure 3). Glass et al further disclose of biochemical assays for screening and identification (i.e. in vitro biological assays), including expression cloning studies (see page 225, right column) to identify potential coactivator compounds such as TR-interaction proteins (TRIPs), which modulate nuclear

receptor function by affecting the transactivation domain (i.e. coactivator binding). Glass et al therefore meet the limitations of the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-16, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Darimont et al (Genes and Development, vol. 12, pp. 3343-3356, 1Nov, 1998), as applied to claims 1-10, 12, 14-16, and 30 above, in view of Kuntz et al (IDS document: Science, vol. 257, pp. 1078-1082, 1992).

The teachings of Darimont et al are set forth above.

Darimont et al do not teach of using high throughput screening to test a library of compounds in their method of modeling, screening, and identifying a test compound that modulates coactivator binding to a nuclear receptor.

Kuntz et al teach that potential ligands can be modeled into binding sites of atomic structural models, of ligand-receptor complexes (see page 1079 under "Structure-Based Design"). Such ligand-receptor interactions can be the basis for identifying ligands with similar backbones that interact with similar interactions. Kuntz et al also teach of large-scale screening (i.e. high throughput screening of a

library of compounds) for rapidly screening and identifying potential ligands (see page 1078 under "Screening"). Furthermore, Kuntz et al teach that the combination of computer modeling and high throughput screening can speed up the time it takes for the discovery of binding ligands (see page 1081, under "Response Time of the Drug Design Cycle").

Given that 1) Darimont et al have taught of methods of identifying a compound that modulates coactivator binding to a nuclear receptor comprising the steps of modeling, screening, and identification, and 2) that Kuntz et al have taught of a combination of computer modeling and high throughput screening of libraries to identify binding compounds, it would have prima facie obvious to one of ordinary skill in the art at the time the invention was made to incorporate high throughput screening method steps into the methods of Darimont et al. One of ordinary skill in the art would have been motivated to combine the modeling and screening steps for identifying a compound of Darimont et al, and using those initial compounds as a starting point for high throughput screening of libraries in view of Kuntz et al teaching the potential advantages of combining the two.

Claims 1, 5, 9-13, 15, and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scanlan et al (International Patent No. WO 97/21993), as applied to claims 1, 5, 9-10, 12, 15, and 17 above, in view of Kuntz et al (IDS document: Science, vol. 257, pp. 1078-1082, 1992).

The teachings of Scanlan et al are set forth above.

Scanlan et al do not teach of using high throughput screening to test a library of compounds in their method of modeling, screening, and identifying a test compound that modulates coactivator binding to a nuclear receptor.

The teachings of Kuntz et al are set forth above.

Given that 1) Scanlan et al have taught of methods of identifying a compound that modulates coactivator binding to a nuclear receptor comprising the steps of modeling, screening, and identification, and 2) that Kuntz et al have taught of a combination of computer modeling and high throughput screening of libraries to identify binding compounds, it would have prima facie obvious to one of ordinary skill in the art at the time the invention was made to incorporate high throughput screening method steps into the methods of Scanlan et al. One of ordinary skill in the art would have been motivated to combine the modeling and screening steps for identifying a compound of Scanlan et

al, and using those initial compounds as a starting point for high throughput screening of libraries in view of Kuntz et al teaching the potential advantages of combining the two.

Claims 1, 5, 9-13, 15, and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over , Glass et al (IDS document: Current Opinion in Cell Biology, vol. 9, pp. 222-232, 1997), as applied to claims 1, 5, 9-10, 12, 15, and 17 above, in view of Kuntz et al (IDS document: Science, vol. 257, pp. 1078-1082, 1992).

The teachings of Glass et al are set forth above.

Glass et al do not teach of using high throughput screening to test a library of compounds in their method of modeling, screening, and identifying a test compound that modulates coactivator binding to a nuclear receptor.

The teachings of Kuntz et al are set forth above.

Given that 1) Glass et al have taught of methods of identifying a compound that modulates coactivator binding to a nuclear receptor comprising the steps of modeling, screening, and identification, and 2) that Kuntz et al have taught of a combination of computer modeling and high throughput screening of libraries to identify binding compounds, it would have prima facie obvious to one of ordinary skill in the art at the time the invention was made to incorporate high throughput screening method steps into the methods of Glass et al. One of ordinary skill in the art would have been motivated to combine the modeling and screening steps for identifying a compound of Glass et al, and using those initial compounds as a starting point for high throughput screening of libraries in view of Kuntz et al teaching the potential advantages of combining the two.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nancy Ogihara whose telephone number is (703) 308-9363. The examiner can be reached Monday-Friday from 8:30-6:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Michael Woodward can be reached at (703) 308-4028.

Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center receptionist, whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 1631 by facsimile transmission. Papers should be faxed to Group 1631 via the PTO Fax Center located in Crystal Park I. The faxing of such papers must conform with the notice published in the Official 1Gazette 1096 OG 30 (November 15, 1989). The CMI Fax Center number is (703) 308-4242.

Nancy Ogihara
June 12, 2000

ARDIN H. MARSCHEL
PRIMARY EXAMINER